REMARKS

The final Office Action dated October 30, 2008 has been reviewed and the following remarks are made in response thereto. Claims 47 - 48 and 51-61 are pending. Claims 49, 50 and 62-65 are withdrawn as being drawn to a non-elected invention. Reconsideration of the instant application is respectfully requested.

I. Rejection Under 35 U.S.C. 103.

Claims 47-48 and 51-61 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 98/30706 in view of Liu *et al.* (1992) *PNAS* 97(26): 283-292 ("Liu"). According to the Office Action, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to produce the construct of WO 98/30706 employing the T-cell epitopes of SEQ ID NOs: 3 and 4, as taught by Liu (Office Action at page 2). Applicants respectfully traverse this rejection.

1. No *prima facie* case established.

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. S*ee, e.g., KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007); *Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); *Abbott Laboratories v. Sandoz, Inc.*, 529 F.Supp. 2d 893 (N.D. Ill. 2007) and MPEP § 2143(A)(1). In addition to demonstrating that all elements were known in the prior art, the Office must also articulate a reason for combining the elements. See, *e.g., KSR* at 1741; *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) citing *KSR*. The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); see, also, *In re Papesh*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963).

Further, the Supreme Court in *KSR* also stated that "a court ***must*** ask whether the improvement ***is more than*** the predictable use of prior art elements according to their established functions." *KSR* at 1740 (emphasis added). As such, the Office must also provide evidence that a reasonable expectation of success existed. MPEP 2143.02. It is further well settled in the law

that teaching away of prior art is a strong indication of nonobviousness. See *e.g. In re Soni*, 54 F.3d 746 (Fed. Cir. 1995).

As will be discussed in detail below, Applicants respectfully submit that in the instant case, no articulated rationale supporting the combination has been provided; in fact, the Liu reference teaches away from the claimed invention and from the combination of Liu with WO 98/30706. Furthermore, no reasonable expectation of success existed at the time the instant application was filed. As such, the asserted *prima facie* case of obviousness fails.

The Office Action states one of skill in the art would have been motivated to combine epitopes of Liu with the construct of WO 98/30706 because Liu teaches that "the epitopes were thought to be involved in the diabetogenic process." OA at 3. As is discussed below, contrary to this conclusion, the actual results Liu obtained suggest that its epitopes were not involved in the diabetogenic process and would not be effective in the presently claimed compositions as Liu's peptides failed even to activate autoreactive T cells in non-immunized NOD mice.

A. Liu teaches away from the claimed invention.

A prior art reference may be considered to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the Applicant. *Monarch Knitting Machinery Corp. v. Fukuhara Industrial Trading Co., Ltd.*, 139 F.3d 1009 (Fed. Cir. 1998), quoting, *In re Gurley*, 27 F.3d 551 (Fed. Cir. 1994). Applicants respectfully submit that one of skill in the art reading Liu at the time the present invention was made would not have been motivated to combine the peptides of Liu with the construct of WO 98/30706, but rather would have been led in a direction divergent from the path that was taken by the Applicants.

Liu immunized one group of NOD mice with the p206 peptide and another group with the p524 peptide. For control Liu used NOD mice that were not immunized with either peptide. Liu then harvested lymph node and splenic cells from the immunized and non-immunized mice and incubated each with recombinant I-A^{g7} complex covalently linked to the p206 or p524 peptide. The mice that had been previously immunized by injection with the p206 and p524 peptides would be expected to generate an immune response—namely antigen-reactive T-cells—to the p206 and p254 peptides as a result of the prior antigen challenge. Despite this, the tet-I-

A^{g7}/p524 tetramer could "barely detect T cells from the p524 immunized NOD mice" at a level of 0.03 – 0.05% that, according to Liu, is not even above the background level (negative control). Liu at page 14599, Col. 2. Furthermore, the tet-I-A^{g7}/p206 tetramer stained only a very small population of CD4+ T cells (0.6 - 1% compared to negative controls). Again, these were mice that had been previously immunized with p524 and p206 peptides and thus staining of reactive T-cells might have been expected given prior exposure to the antigens. Yet with respect to the p524 peptide no staining above background was observed and with respect to the p206 peptide only a very small population of CD4+ T cells were stained compared to negative control.

Moreover, in the *spontaneous* NOD mice that had not been immunized, "tetramer staining results showed that the tetramers detected T cells infiltrating the islets of NOD mice with a percentage that is not significantly above the background..." Liu at page 14600, Col. 1. Therefore, Liu's results indicate that p206- and p524-reactive T cells are not spontaneously present in NOD mice at detectable levels. *Id.* Type 1 diabetes is a spontaneous disease, not one that is thought to be initiated by immunization with an antigen. Based on Liu's results (barely staining for only one peptide in immunized mice and no staining for either peptide in non-immunized mice), one of skill in the art would not have thought the p206 and p524 peptides were involved in activation of autoreactive T cells during development of diabetes. As such, a person of ordinary skill in the art reading Liu at the time of Applicants' invention would not have had any motivation to use the p206 or p524 peptides for insertion into the construct of WO 98/30706. Instead, such a person would have been led in a direction divergent from the path that was taken by the Applicant since the p206 and p524 peptides failed to even activate autoreactive T cells in non-immunized NOD mice. Again, teaching away is a strong indication of non-obviousness.

Since Liu teaches away from the presently claimed invention, no *prima facie* case of obviousness has been established. Withdrawal of the instant rejection is respectfully requested.

B. No reasonable expectation of success.

As discussed above, in addition to showing that all elements of a claim were known in the prior art and that one of skill had a reason to combine them, the Office must also provide evidence that a reasonable expectation of success existed. MPEP 2143.02. This is an essential component of a *prima facie* case of obviousness and one which has not been established. As will be discussed in detail below, given both the negative results of Liu (discussed above) and the

nature of the test model used in WO 98/30706, one of skill in the art would not have had any expectation of success in combining the peptides of Liu with the construct of WO 98/30706 at the time of Applicants' instant invention, let alone any reasonable expectation of success.

Liu

As is discussed in detail above, a person of ordinary skill in the art reading the Liu paper at the time Applicants' invention was made would not have selected the p206 and p524 peptides for insertion into the construct of WO 98/30706. Even assuming, *arguendo*, such a person had motivation to select these peptides (which is not admitted), they would not have had a reasonable expectation of success at treating or preventing type 1 diabetes. Again, in Liu mice that had been previously immunized by injection with the p206 and p524 peptides, the tet-I-A^{g7}/p524 tetramer could "barely detect T cells from the p524 immunized NOD mice" at a level of 0.03 – 0.05% that may not even be regarded as above the background level. Liu at page 14599, Col. 2. Furthermore, the tet-I-A^{g7}/p206 tetramer stained only a very small population of CD4+ T cells (0.6-1% compared to negative controls). Furthermore, both the tet-I-A^{g7}/p524 tetramer and the tet-I-A^{g7}/p206 tetramer failed to detect T cells from non-immunized NOD mice at all. On at least this basis, one of skill in the art reading Liu and WO 98/30706 at the time of Applicants' instant invention would not have had a reasonable expectation that combining the peptides of Liu with the construct of WO 98/30706 would provide an agent useful for treatment or prevention of type 1 diabetes. Since the peptides of Liu did not detect T cells from non-immunized NOD mice and barely detected T cells for only one of the peptides in previously immunized mice, they would not be expected to function to treat or prevent diabetes in the presently claimed compositions.

WO 98/30706

The Office Action relies on WO 98/30706 which discloses a fusion protein having the proteolipid protein (PLP) autoantigen inserted into the D segment of a CDR3 loop. PLP is an autoantigen associated with multiple sclerosis. Even if a person of ordinary skill in the art had motivation to use the peptides of Liu (which, as is discussed above, they did not), Applicants respectfully submit that the multiple sclerosis test model used in WO 98/30706 (experimental allergic encephalomyelitis) is far different from the type 1 diabetes NOD mouse model used in examples within the instant application such that any success or failure shown in WO 98/30706

in the MS model would not be at all predictive of success or failure of such a fusion protein in treatment or prevention of type 1 diabetes.

Specifically, the relevant examples in WO 98/30706 (*e.g.* Examples I and XI) involve induction of an immune response with a ***known*** pathogenic peptide (PLP1) followed by treatment of the induced immune response with a slightly altered version of the ***very same peptide*** (PLP-LR) introduced in the form of a chimeric antibody immunomodulating agent. PLP-LR is an analog of PLP1 in which Trp144 and His147 are replaced with Leu and Arg, respectively. Therefore, in Examples I and XI of WO 98/30706, a disease state is induced with a known pathogenic peptide and then treated with a slightly altered non-pathogenic version of the very same peptide.

In stark contrast to those examples, the onset of type 1 diabetes in the NOD mouse model is a *spontaneous* event not triggered by administration of a known peptide antigen. Because the inducer peptide is not known, it was completely unpredictable at the time the present invention was made which peptide antigen, if any, when incorporated into compositions disclosed in the instant application, would have any impact on type 1 diabetes, let alone delay or prevent that disease state. Particularly when the peptides of Liu could not even detect CD4+ T Cells in non-immunized NOD mice. This is very different from the situation in WO 98/30706 in which the disease inducing peptide was known at the outset, and treatment was provided with a slight variation of the very same inducer peptide. In view of these significant differences and the highly unpredictable area of art of the presently claimed invention, a person of ordinary skill in the art at the time the present invention was made would not have had a reasonable expectation of success in treating or preventing type 1 diabetes.

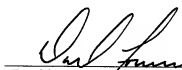
For at least the foregoing reasons, a person of ordinary skill in the art would not have had any expectation of success, let alone any reasonable expectation of success. As such, no *prima facie* case of obviousness has been established. Withdrawal of the instant rejection is therefore respectfully requested.

Conclusion:

Applicants respectfully submit that in the instant case, no motivation to combine references and no reasonable expectation of success existed at the time of Applicants' instant invention. As such, Applicants respectfully submit that the asserted *prima facie* case of obviousness fails.

The application is believed to be in condition for allowance. Early and favorable considerations is respectfully requested. The Commissioner is hereby authorized to charge deposit account 02-1818 for any fees which are due and owing.

Respectfully submitted,



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